Remarks/Arguments

Claims 119-123 are pending in this application.

I. 35 U.S.C. §§ 101 and 112, First Paragraph –Utility/Enablement

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 170 starting on page 539 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO1153 gene for patentable utility of the claimed PRO1153 polypeptides. This data is clearly disclosed in the instant specification in Example 170, which discloses that the gene encoding PRO1153 showed significant amplification in primary lung tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly over expressed and has utility, along with the antibody that binds it, in the diagnosis of lung cancers or for individuals at risk for developing lung cancer.

The Examiner asserts that basis of the rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. (Page 3 of the instant Final Office Action).

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, Applicants have submitted, in their Response filed October 27, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung and colon cancers, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Second, Applicants have submitted, in their Response

filed June 16, 2004, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Third, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, the art overwhelmingly shows that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed and has utility, along with the antibody that binds it, in the diagnosis of lung cancers.

Applicants further submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Applicants' Response filed June 16, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO1153 polypeptides and the antibodies thereto are useful as a diagnostic tools for detecting lung tumors.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO1153 polypeptides.

The Examiner has asserted that "lung cells can be aneuploid without the presence of cancer" and cites references by Hittelman et al. and Sen et al. in support of the assertion that " it is not clear that PROl153 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium." (Page 4 of the instant Final Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed June 16, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Regarding Sen and Hittelman, Applicants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* in fact support the Applicants' position that PRO1153 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in lung cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lung lesions which may eventually lead to lung cancer. Many articles published around the effective filing date of this application studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of lung cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

The Examiner has asserted that significant further research is would have been required of the skilled artisan to reasonable confirm that PRO1153 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, thus the asserted utility is not substantial. (Page 8 of the instant Final Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Applicant has identified for the invention that can be viewed as

providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[2] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO1153 is significantly amplified in certain lung tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1153 gene is amplified, the PRO1153 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO1153 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1153 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed antibodies to the PRO1153 polypeptide, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO1153 polypeptide expression and that the claimed antibodies to the PRO1153 polypeptide have utility in the diagnosis of cancer.

The Examiner asserts that "the instant disclosure does not show reliable fluorescence of PRO1153 even within the same experimental group. In addition, the instant Specification does not provide proper statistical analysis such as reproducibility, standard error rates, etc." (Page 6 of the instant Final Office Action).

Applicants submit that the Examiner is applying a standard that is not legally correct. The law, as it is reflected in the M.P.E.P. and the Utility Guidelines does not require that the

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[1] M.P.E.P. §2107.01.

[2] M.P.E.P. §2107 II(B)(1).

Applicant show a positive result in a statistically large percentage of the tissue samples studied in order to make an assertion of utility. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO1153 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott* v. *Finney,* 34 F.3d 1058, 1063,32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson* v. *Bowler,* 626 F.2d 853,856,206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Further, the Goddard Declaration was presented to show what delta Ct values were considered significant in the TaqMan" assay. The deltaCt values for PR01153 of at least 1.01-1.52 deletaCt units which corresponds to $2^{1.01}$ -$2^{1.52}$ -fold amplification or 2.013-fold to 2.868 -fold amplification in adenocarcinomas or squamous cell carcinomas of the lung, were considered significant according to the Goddard declaration. The formula for showing how the data was analyzed has been clearly disclosed in the specification in Example 170, page 539. As explained in the passage on page 539, lines 37-39, "the results of TaqMk™ PCR are reported in ~Ct units. One unit corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1153 showed approximately 1.01-1.52 deltaCt units which corresponds to $2^{1.01}$ -$2^{1.52}$ -fold amplification or 2.013-fold to 2.868 -fold amplification in adenocarcinomas or squamous cell carcinomas of the lung.

The Examiner has further asserted that " Only about 6% of the experimental samples tested positive, even within each tumor type and subtype." (Page 8 of the instant Final Office Action)

Appellants respectfully point out that they have shown significant DNA amplification in two different adenocarcinomas and squamous cell carcinomas of the lung. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even with most tumors. For example, the article by Hanna and Mornin (submitted with the Response filed June 16, 2004), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1).

Appellants submit that the amplification of the PRO1153 nucleic acids in even one lung tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung tumor in which it was amplified. Appellants further note that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung or colon tumor, whereas absence of amplification would be non-conclusive. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker. If the goal is to diagnose lung cancer, then contrary to the Examiner's assertion, a positive result does indicate the presence of cancer, while a negative result is not conclusive, and requires follow up testing.

The Examiner is also apparently concerned that no mutation or translocation of PRO1153 has been associated with a cancer. The Examiner further asserts "there is no disclosure regarding what treatment modality should be chosen by the clinician based on

whether or not the PRO1153 gene is overexpressed." (pages 7-8 of the instant Final Office Action).

However, knowledge of a mechanism of action is not required to discover the utility of a cancer diagnostic. Applicants note that overexpression of cancer markers is presently used in the diagnosis of, and in guiding the treatment of, cancer patients (see, e.g., Hanna and Mornin, of record).

Applicants further cite Hyman *et al.* ("Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002), of record), which discloses studies of gene amplification. One of the genes found to be amplified, HOXB7, was found to show "a clinical association between HOXB7 amplification and poor patient prognosis." (Page 6244, col.1 to col.2). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. Applicants also cite Pollack *et al.* ("Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002), of record), wherein these authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

A *prima facie* case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that Haynes et al., Pennica, et al, Konopka, et al, Godbout, et al, and Li, et al. are no longer being relied upon to support the rejections. Nevertheless, the Examiner cites Hittelman et al. and Hu et al. to support the assertion that "gene amplification data presented is not a reliable indicator of disease." (page 3 of the instant Final Office Action).

As a preliminary matter, Applicants reiterate that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to

be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Applicants' arguments presented in the previously filed Responses are hereby incorporated by reference in their entirety.

Hu *et al.*

The Examiner has further cited Hu et al., in support of the assertion that "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 5 of the instant Final Office Action).

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants submit that Hu *et al.* does not conclusively show that it is more likely than not that gene amplification does not result in increased expression at the mRNA and polypeptide levels. First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based on a statistical analysis of the information disclosed in the published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on the MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array

analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants first submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not gene amplification data. Therefore, their findings would not be directly applicable to gene amplification data. In addition, Applicants respectfully submit that the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes is typical.

According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes."[3] Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation reflects only the current research interest of a molecule rather than the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very

[3] *Id.*

unreliable standard and that their research does not provide any meaningful information regarding the correlation between microarray data and the biological significance of a molecule.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently."[4]

In summary, the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1153 has utility. As discussed above, the law does not require that DNA amplification is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have incrased mRNA and protein levels

As discussed above and in detail previously, Applicants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100 references and Declarations by experts in the field of oncology and gene expression, i.e.: the

[4] *Id.* (emphasis added).

Declarations by Dr. Audrey Goddard, Dr. Paul Polakis (I and II) and Dr. Avi Ashkenazi, to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

The Examiner asserts that "[i]n order for PRO1153 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1153 mRNA or PRO1153 polypeptide levels in lung tumors have been brought forth on the record." (Page 4 of the instant Final Office Action).

The Examiner's reference to the lack of necessary correlation or accurate prediction in some of the rejections clearly shows that the Examiner again applies an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. As discussed below, the references cited by the Examiner do not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels.

In contrast, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed June 16, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, as the Examiner has acknowledged, the art teaches that, in general, there is a correlation between mRNA levels and polypeptide levels.

Accordingly, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed. Thus, the claimed antibodies to the PRO1153 polypeptide have utility in the diagnosis of cancer.

Applicants therefore respectfully request withdrawal of the rejections of Claims 119-123 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **50-4634** Attorney Docket No.: **123851-181895 (GNE-2730P1C32)**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 10, 2008

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